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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER
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ART UNIT	PAPER NUMBER
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DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

# Office Action Summary

Application No.

09/423.622

Applicant(s)

MULLER ET AL.

Examiner

Bridget E. O'Laughlin-Bunner

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1647

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

## Status

- 1) ☐ Responsive to communication(s) filed on 21 September 2000.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☐ Claim(s) 1-17 is/are pending in the application.
- 4a) Of the above claim(s) 15-17 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☐ Claim(s) 1-14 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claims 1-17 are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are objected to by the Examiner.
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved.
- 12) ☐ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. § 119

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
- a) ☒ All b) ☐ Some \* c) ☐ None of the CERTIFIED copies of the priority documents have been:
1. ☐ received.
2. ☐ received in Application No. (Series Code / Serial Number) \_\_\_\_\_.
3. ☒ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

## Attachment(s)

- 15) ☒ Notice of References Cited (PTO-892)
- 16) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 6
- 18) ☐ Interview Summary (PTO-413) Paper No(s) \_\_\_\_\_
- 19) ☐ Notice of Informal Patent Application (PTO-152)
- 20) ☐ Other:

## **DETAILED ACTION**

### ***Status of Application, Amendments and/or Claims***

The preliminary amendment of 08 February 2000 (Paper No. 5) has been entered in full.

### ***Election/Restrictions***

Upon further consideration, Groups I and II of the restriction in Paper No.7 have been rejoined.

Applicant's election with traverse of the species of basal membrane building elements in Paper No. 8 is acknowledged. The traversal is on the ground(s) that the basal membrane building elements are not recited in any of the claims falling in the elected Group II of the restriction requirement. This is not found persuasive because the prior restriction/election requirement made by the examiner included claim 2 in the invention of Group II. Claim 2 recites application of an inhibitor substance to prevent synthesis or assembly of basal membrane building elements.

Claims 1-14 are under consideration in the instant application.

### ***Information Disclosure Statement***

The information disclosure statement filed 11 February 2000 was received and complies with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609. It has been placed in the application file and the information referred to therein has been considered as to the merits.

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### ***Specification***

The specification of the current application does not conform to the guidelines listed below. More specifically, there are no headings to differentiate between the sections of the specification.

The following guidelines illustrate the preferred layout and content for patent applications. These guidelines are suggested for the applicant's use.

### **Arrangement of the Specification**

The following order or arrangement is preferred in framing the specification and, except for the reference to "Microfiche Appendix" and the drawings, each of the lettered items should appear in upper case, without underlining or bold type, as section headings. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

- (a) Title of the Invention.
- (b) Cross-References to Related Applications.
- (c) Statement Regarding Federally Sponsored Research or Development.
- (d) Reference to a "Microfiche Appendix" (see 37 CFR 1.96).
- (e) Background of the Invention.
  - 1. Field of the Invention.
  - 2. Description of the Related Art including information disclosed under 37 CFR 1.97 and 1.98.
- (f) Brief Summary of the Invention.
- (g) Brief Description of the Several Views of the Drawing(s).
- (h) Detailed Description of the Invention.
- (i) Claim or Claims (commencing on a separate sheet).
- (j) Abstract of the Disclosure (commencing on a separate sheet).
- (k) Drawings.
- (l) Sequence Listing (see 37 CFR 1.821-1.825).

The disclosure is objected to because of the following informalities:

- a. The specification contains no section headings.
- b. On page 1, lines 23-26, the sentence, "As useful agents are addressed neutralizing..." should be reworded without adding new matter. The meaning of the sentence is not clear and concise.

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c. The beginning of the paragraph on page 3, lines 21-34, is not clear and concise.

Words should be added or removed so the meaning of the paragraph can be understood.

d. The sentence on page 6, lines 31-35, stating "on failure of adult mammalian CNS axons we examined..." is not clear and concise. A word or phrase should be added at the beginning of the sentence so the topic can be understood.

e. On page 9, line 34, the term "regenerating animals" does not have a clear meaning. It could mean "animals that have been regenerated" or in relation to the application, "animals with regenerated axons". This term should be defined or different terminology inserted.

f. On page 12, line 5, the first sentence is not a complete sentence because a verb is missing. It is not clear if this sentence is supposed to be a heading or a sentence. A possible suggestion would be to insert "were performed" after the word "injections" or to make "electrophysiology and biocytin injections" bolded.

g. On page 12, lines 10-11, the sentence, "Stimuli: 100  $\mu$ s, 5-20 V were delivered via a bipolar tungsten electrode" is not clear and concise. The sentence should be reworded so the type and amount of stimuli delivered can be further understood.

Appropriate correction is required.

### ***Claim Objections***

Claims 5 and 14 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to

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cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claims 5 and 14 recite the method of claims 4 and 13 wherein the inhibitor substance is selected from a listed group. The inhibitor substances listed in claims 5 and 14 do not further limit the inhibitor substances listed in claims 4 and 13. Applicant elected iron chelating agents from claims 4 and 13 to be the inhibitor substance examined in the instant application. Therefore, claims 5 and 14 could be amended to further limit claims 4 and 13 by listing iron chelating agents.

### ***Claim Rejections - 35 USC § 101***

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 10-14 provide for the use of a method for the improvement of neuronal regeneration by prevention or inhibition of basal membrane formation, but, since the claims do not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 10-14 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd. v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

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*Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for enhancing fornix axonal regeneration by administering a basal membrane inhibitor, more specifically an iron chelator, to injured neuronal tissue, does not reasonably provide enablement for generically improving neuronal regeneration comprising prevention or inhibition of basal membrane formation induced by a lesion of neuronal tissue. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 1-3, 7-8, and 10-12 are directed to a method for the improvement of neuronal regeneration comprising inhibiting basal membrane formation caused by a lesion in the neuronal tissue. The inhibitor substance (medicament) used to inhibit basal membrane formation is applied intraventricularly, systemically, orally, or intravenously. The scope of patent protection sought by Applicant as defined by the claims fails to correlate reasonably with the scope of the enabling disclosure for the following reasons.

The specification proposes a method "for the improvement of neuronal regeneration, a medicament for the improvement of neuronal regeneration and use of a specific inhibitor substance." The specification discloses on page 1 that the method of the invention can be used to

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"prevent, suppress, or treat scar formation in the CNS". However, the specification does not teach the region of the CNS, which encompasses the brain and spinal cord, that the methods are applicable to. Therefore, it was assumed that the invention could be applied to both brain and spinal cord injuries. It is noted that page 6 states "the mechanically transected postcommissural fornix of the adult rat...was used to determine whether specific biochemical or immunochemical modulation of BM formation would provide a means to stimulate axon regeneration". The specification does not provide any experiments or examples showing that the method of the invention can be successfully applied to spinal cord lesions. Although both CNS components, the brain and the spinal cord may respond differently to the same form of treatment and also may require different doses of the inhibitor substance. Further, the specification does not disclose exactly what neurons are being targeted for axonal regeneration. There are a variety of neurons that may/may not be affected by the invention, such as motor neurons, sensory neurons, glial cells, and oligodendrocytes. Overall, there is no enabling disclosure guiding one how to "prevent, suppress, or treat scar formation" of lesions of the spinal cord or which neuronal axons are being successfully regenerated.

The state of the art is such that numerous problems exist in regards to effectively "regenerate" neurons in a subject (i.e., as it relates to claims 1 and 10). Problems encountered before one can begin to assess whether treatment with "an inhibitor substance" can occur within the CNS include: 1) neuronal cell injury often results in cell death and 2) administration of inhibitor substances to treat/regenerate neurons requires solutions to not only bypass the blood-brain barrier (i.e. as it relates to claims 7 and 8), but to selectively target the lesion site and responsive neurons with enough of the inhibitor substance to maintain /regenerate neural



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pathways. Further, the instant specification provides no guidance on when to treat a subject for "prevention" of basal membrane formation encompassed by the current claims. The specification also provides no guidance on any functional assays to extrapolate when such treatment is effective in preventing basal membrane formation. The disclosure does not state when the inhibitor substance should be slowed or stopped in a subject who has incurred a CNS lesion, without undue experimentation to determine such.

It is also well known in this unpredictable art that regeneration does not occur in the CNS either because processes fail to grow the necessary distance, they are in competition with other nearby neuronal processes not derived from the affected nerve, astrocytic scarring blocks axonal elongation, or because of misdirected axonal growth (e.g., see Jackowski, pgs. 309-310 and pg. 305, last *pp*). Accordingly, because of the lack of guidance provided by the specification as to how one can rescue dead or dying cells instantaneously affected, for example, by a head injury, and because damaged neurons die unless "functional synaptogenesis" prevents neuronal death, there is no nexus that merely adding an iron chelating agent to a lesion site *in vivo* can reasonably be extrapolated to successfully treat any human subject experiencing neurodegeneration, as claimed, without undue experimentation to determine such.

Due to the large quantity of experimentation necessary to improve neuronal regeneration comprising prevention or inhibition of basal membrane formation induced by a lesion of neuronal tissue, the lack of direction/guidance presented in the specification regarding the "prevention" of basal membrane formation, when the inhibitor substance should be stopped or slowed, and how to rescue dead and dying cells, the absence of working examples directed to prevention or inhibition of scar formation of the spinal cord, the complex nature of the invention,

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the unpredictability of axon regeneration, and the breadth of the claims which fail to recite limitations on the region of the CNS affected and the type of neuronal cells that sprout axons, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 provides for the use of a method for the improvement of neuronal regeneration by prevention or inhibition of basal membrane formation, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Regarding claims 4-6, 9, and 13-14, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim

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does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claims 4-6, 9, and 13-14 recite the broad recitation of general inhibitor substances or growth promoting proteins and therapeutically effective amounts of inhibitor, and the claims also recite specific examples or species of each general inhibitor or growth promoting protein and dosage ranges of inhibitor, which is the narrower statement of the range/limitation.

Regarding claim 6, the phrase "like" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claims 1-2 and 10-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite because it is unclear whether open or closed term language is intended. See MPEP § 2111.03. Claims 1-2 and 10-11 are further indefinite because the scope of the claims cannot be determined with respect to what unrecited additional components or steps, if any, are excluded from the scope of the claim.

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Claims 3-5 and 12-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite because the inhibitor substances recited in the claims do not constitute proper Markush groups. See MPEP § 2173.05(h). Claims 4-5 and 13-14 are further indefinite because the scope and clarity of the claims is uncertain.

Claims 5 and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite because a claim that depends from a claim which "consists of" the recited elements or steps cannot add an element or step. See MPEP § 2111.03.

Claims 6 and 7 recite the limitation "inhibitor substances" on page 2 of the claims, lines 11 and 17. There is insufficient antecedent basis for this limitation in the claims.

Claims 7 and 8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite because the claims do not resolve the 35 U.S.C. 112, second paragraph, issues of claim 1.

### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3 and 10-12 are rejected under 35 U.S.C. 102(b) as anticipated by Logan et al (WO 93/19783). Logan et al. teaches a method for the prevention, suppression, or treatment of a central nervous system (CNS) pathology, such as scar formation, characterized by accumulation of extracellular matrix in a tissue by contacting the tissue with an agent that inhibits the extracellular matrix producing activity of TGF- $\beta$  (pg 1-4). Logan et al. discloses the inhibition

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of extracellular matrix formation by applying inhibitors of TGF- $\beta$  to a vertical lesion made in the occipital cortex, corpus callosum, and presubiculum of a rat (pg 11, lines 29-32). Logan et al. also teaches a pharmaceutical composition containing agents that inhibit the activity of TGF- $\beta$  which can be administered to a patient to prevent, enhance, or treat CNS scar formation (pg 10, lines 10-28). One of the components of the extracellular matrix (ECM) is the basal membrane (BM), which is a three layered structure, with a prominent layer being the basal lamina. TGF- $\beta$  is a growth factor that stimulates the synthesis of individual ECM components, such as fibronectin and collagens. Therefore, the inhibition of TGF- $\beta$  in neuronal tissue inhibits the formation of collagen and in turn, the basal membrane.

Claims 1 and 6 are rejected under 35 U.S.C. 102(b) as being anticipated by Grumet (WO 95/13291). Grumet teaches a method comprising administration of Ng-CAM (a large neuronal cell adhesion molecule that binds extracellular matrix molecules) in combination with an effective amount of at least one other agent that is capable of promoting neuronal survival, growth, differentiation, or regeneration in lesions in the central nervous system (pg 8, lines 10-28). Examples of additional agents included nerve growth factor (NGF) and brain-derived neurotrophic marker (BDNF). Briefly, the cell adhesion molecule, Ng-CAM, neutralizes the inhibitory effects of extracellular matrix molecules such as chondroitin sulfate proteoglycans (e.g. neurocan and 3F8 proteoglycan (PG)), which inhibit nerve regrowth and neuronal cell division (pg 15, lines 31-32).

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***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102((e), f) or (g) prior art under 35 U.S.C. 103(a).

Claims 4-5 and 13-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Logan et al. (WO 93/19783) in view of White and Kraus (Annals of Emergency Med. 22:970-979) and Kivirikko et al (FASEB J. 3:1609-1617). Logan et al. teaches a method for the prevention, suppression, or treatment of a central nervous system (CNS) pathology, such as scar formation, characterized by accumulation of extracellular matrix in a tissue by contacting the tissue with an agent that inhibits the extracellular matrix producing activity of TGF- $\beta$  (pg 1-4). Logan et al. also discloses the inhibition of extracellular matrix formation by applying inhibitors

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of TGF- $\beta$  to a vertical lesion made in the occipital cortex, corpus callosum, and presubiculum of a rat (pg 11, lines 29-32).

Logan et al. does not teach a method for the prevention, suppression, or treatment of a CNS lesion by contacting the injured tissue with an inhibitor substance, specifically an iron chelating agent.

White and Kraus teaches that several classes of pharmacologic agents had potential for use in limiting injury progression and stimulating repair after blunt closed-head injury, including iron chelators (pg 975, column 2).

Kivirikko et al. teaches several compounds that inhibited the enzyme, prolyl 4-hydroxylase, which catalyzes the formation of 4-hydroxyproline in collagens. 4-hydroxyproline is an essential component for collagen triple helix formation (pg 1609). The two compounds that most effectively inhibited prolyl 4-hydroxylase were pyridine 2,4-dicarboxylate and pyridine 2,5-dicarboxylate (pg 1612, column 2).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the Logan et al. method for the prevention, suppression, or treatment of a central nervous system (CNS) lesion by utilizing another inhibitor (other than TGF- $\beta$ ) that inhibited accumulation of extracellular matrix, such as those taught by White and Kraus and Kivirikko et al., who disclose that iron chelators, such as pyridine 2,4-dicarboxylate and pyridine 2,5-dicarboxylate, could have been used to limit injury progression in head trauma by inhibiting collagen accumulation. The person of ordinary skill in the art would have been motivated to make that modification because iron chelators would have allowed faster penetration of the blood-brain barrier (White and Kraus, pg 976) and may have caused fewer

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unwanted side affects compared to other compounds. The person of ordinary skill in the art would have expected success because iron chelators, such as 2,4-dicarboxylate inhibited hepatic collagen accumulation in rats with carbon tetrachloride-induced liver injury (Kivirikko et al., pg 1613, column 2). Therefore, the claimed invention as a whole was clearly *prima facie* obvious over the prior art.

### ***Conclusion***

The art made of record and not relied upon is considered pertinent to applicant's disclosure.

U.S. patent 4,717,727 (Gunzler et al.)

U.S. patent 5,082,926 (Chelberg et al.)

U.S. patent 5,250,414 (Schwab et al.)

WO 96/00582 (Sarras et al.)

Kruczewski, R. et al. Glial response to transection of the rat postcommissural fornix. *European J. of Neuroscience* 55: 190, 1992.

Stichel, C.C. et al. Inhibition of collagen IV deposition promotes regeneration of injured CNS axons. *J. of Neuroscience* 11: 632-646, 1999.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. O'Laughlin-Bunner whose telephone number is (703) 305-7148. The examiner can normally be reached on 8:30-5:00 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the



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organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Bridget O'Laughlin-Bunner  
Art Unit 1647  
November 2, 2000

*Elizabeth C. Kemmer*